Refer to: Scoggin CH: The cellular basis of aging (Medical Progress). West J Med 135:521-525, Dec 1981

Medical Progress

The Cellular Basis of Aging

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Normal cells have only a finite life span before they die. The process known as aging may occur as a result of continued damage to the cell or as a result of expression of predetermined information within the genetic structure of the cell. Both processes lead to progressive cellular dysfunction which is evidenced by the organs of the body as aging. By understanding how individual cells age we will gain insight into how the body as a whole ages. The impact of such knowledge on science and society is a matter of both conjecture and concern.

THE CHANGES of the body which occur with aging are well known. Wrinkling of skin, graying of hair, lessened muscular strength, and diminished sensory functions such as decreased vision and hearing are almost universal phenomena. Other consequences of aging are less predictable. For instance, many persons remain mentally sharp well into their 80's while others will display progressive dementia as early as the sixth decade of life. Because aging is a universal human experience it has been a constant area of scientific inquiry. The study of the basis of the process of aging has been termed "biogerontology."

The aging process is evident within the cells of the body. As cells age there is a decline in vital functions such as oxidative phosphorylation.[1] Studies of β-adrenergic receptors of cells show decreased adrenergic responsiveness.[2] Such findings may account for decreased ability with old age to tolerate stress and exercise. Decreased cellular production of molecules vital for function occurs with aging. DNA synthesis has been shown to decline appreciably in aging WI-38 fibroblasts.[3] RNA synthesis decreases in aging cells.[4] Incorporation of radiolabeled amino acids into proteins dwindles with age of the cell.[5] Interestingly, lipid synthesis is less affected by aging than production of DNA, RNA and proteins.[6] Since the cells make up the organs that constitute the body, changes in cellular function are reflected in alterations of the organs and body. This review starts from predication that the structural and functional basis of the somatic phenomena recognized as a consequence of aging lie within the cells of the body. Understanding how cells age will lead to insight into how the body as a whole ages. Certainly such knowledge of cytogerontology[7] should help us to deal with the consequences of aging. Whether or not such perceptions will eventually lead to measures to reverse or arrest the present inevitability of the process is speculation.

In general, it is thought that the changes associated with aging of cells may occur through two major mechanisms. Progressive damage to the cell, either from external or internal factors, may lead to accumulative cellular dysfunction which

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This work was supported in part by a New Investigator Award (1 R23 HD 14567 01A1) from the National Institute of Child Health and Human Development.

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is manifest in the intact individual person as aging. The second factor which is of importance is the genetic information within the cell. While many theories have been proposed it is probable that there is no single cause of aging; therefore, both major mechanisms probably jointly contribute to the final process of aging.

Aging as a Consequence of Progressive Cellular Damage

It is possible that aging of cells may be the consequence of "wear and tear." This type of damage may arise as a result of damage from elements outside of the cell or by damage from factors within the cell. Most investigations have focused on damage to the DNA and protein mechanisms of cells.

Damage to Cells by External Environmental Factors as a Cause of Aging

It has been suggested that toxic factors within the environment may lead to progressive damage of the genomic information of cells. The possible effect of background irradiation is an example.[8] Background irradiation may act to damage chromosomes or single genes either mutating or inactivating them. Accumulated damage would eventually be expressed as absent or abnormal gene products. Alterations in normal gene function would lead to the changes of cellular activity associated with age. It has been proposed that as the errors of cellular function accumulate, they eventually summate to form the "error catastrophe" which results in death.[9] Some would speculate that many environmental factors may play a role in changing gene expression with age. While in the modern world infection plays a less prominent role, it is possible that chemical and other toxic factors within the environment may have a harmful effect on the genome of a cell. Thus, the effect of environmental stress would lead to progressive damage to cells, particularly the genes which are the primary source of information for cells, leading to the changes in the whole organism which we recognize as aging. However, it is important to stress that abnormalities of gene function have yet to be shown to be a correlate of aging in humans. Likewise, chromosomal changes have not been associated with aging in humans. In fact, changes of the chromosomal makeup of cells (aneuploidy) is an almost constant feature of cells with a seemingly infinite life span—malignant cells. Epidemiological association between exposure to environmental toxins, radioactivity or other factors that may alter cell function have not been established.

When suggesting that "wear and tear" may result in aging, it is not necessary to ascribe all the impact of "wear and tear" to be on the chromosomal and protein synthesizing mechanisms of the body. In areas of the body such as the angle of the jaw and elbows there is progressive loss of elasticity and thinning of the skin. The changes may just represent the consequences of usage. Unlike cells that are very active metabolically, the connective tissue that serves as a framework for tissue is relatively static. Thus the continuous extension and relaxation of the fibers may lead to progressive degeneration from the effects of such stress alone. Exposure to sunlight may accentuate such degeneration.[10]

Aging Due to Cellular Damage by Factors Internal to the Body

Certain products of metabolism toxic to cells may escape the normal cellular degradative processes. These factors may cause damage of cells which leads to the changes of age. This would be a process similar to gradual accumulation of harmful by-products of combustion in an automobile engine. With time, progressive dysfunction and eventual failure of the machine occurs. Two classes of substances are examples of this potential cause of aging in living organisms. Aldehydes bind to molecules such as DNA and enzymes to irreversibly inactivate them. It has been proposed that the increased cross-linking of collagen seen with aging is due to the effect of aldehydes.[11]

Free radicals of oxygen are another product of cellular metabolism that may damage biological tissues, and have been proposed as playing a prominent role in the aging process.[12] They arise from a number of reactions within cells and are a result of normal oxidative metabolism of organic compounds by molecular oxygen. The oxygen radicals which are produced include singlet oxygen, superoxide radical, hydroxyl radical and hydrogen peroxide. These oxygen species are highly reactive and can alter most types of cellular macromolecules. They have been shown to peroxidize unsaturated fatty acids, oxidize proteins, damage nucleic acids and cleave polysaccharides.[13] When these radicals are generated in the media surrounding cells in tissue culture, they can kill and lyse cells. We have found that hydrogen peroxide appears to be the primary oxygen

radical that causes fatal injury to human cells in tissue culture.[14] It is possible that the other radicals of oxygen play a more prominent role in the intracellular damage of human cells.[15] It has been suggested that in aging the progressive accumulation of damage from such reactive radicals may lead to diminution of cellular function and tissue integrity which we recognize as aging. It is to be emphasized that the possible roles of free radicals in the aging process remain speculative. It has not been shown that the level of free radicals increases with aging nor have the levels of free radicals been shown to be higher in animals with short life spans than in animals with long life spans.[16] Should, however, the effect of free radicals be substantiated, it would suggest some interesting therapeutic possibilities. This is because there would be possible ways to bolster cellular defense against oxygen radical challenge. Antioxygents such as vitamin E, superoxide dismutase, catalase and methyl sulfoxide might have benefit.[17] To date there is no scientific information to support the use of such compounds as panaceas against the aging process.

Genetic Predetermination to Aging

Regardless of the possible impact of factors from without or within that serve to damage cells, the normal cell itself has only a finite life span of approximately 50 doublings before it is no longer capable of replication.[18] This innate senescence cannot be overcome by placing the cell in a protected or "young" environment. Animal transplantation experiments have shown that transplantation of "old" cells into young inbred recipients does not change the cell life expectancy.[19] Furthermore, the determination of the finite life of cells appears to lie within the cell nucleus. Fusion of cytoplasm from young cells with nuclei of old cells (and vice versa) leads to a hybrid cell whose longevity is determined by the parent nuclei, not cytoplasm.[20] However, even though the number of replications of human cells is finite, it is probable that aging is not the result of cells losing their proliferative capacity, rather it has been proposed that within the human genome exists a predetermined program to progressively slow down or shut down the physiologic phenomenon of the body.[21] The information to do this may differ from cell-type to cell-type within the body. Individual differences may occur. In one person wrinkled skin may develop as an obvious manifestation of aging while dementia develops in another. Thus the genome would be much like a tape that plays out a scenario that we recognize as aging. The transition from youth to age would simply be a programmed translational event of our genetic information. A genetic link with aging is supported by studies of twins that show an hereditary influence on life expectancy,[22] and investigations that have demonstrated an association between the major histocompatibility complexes and aging.[23]

What Unifies Our Current Concepts of Aging?

As mentioned before, there is no one theory of aging that is universally accepted. There do appear to be some unifying features in the mechanisms discussed above. One feature is that genetic instability is a prominent cause of aging. While genetic predeterminism would make it inevitable that aging and eventual failure of the organism would occur, it is obvious that all individuals of a species within the same environment do not age at identical rates. We speak of "mean life expectancy" which is very similar to the term "mean time to failure" used by Hayflick.[21] What this implies is that the rate at which we age varies from person to person because the genetic tape is longer or shorter (thus the tendency of families to be long-lived or short-lived) or because its translation is either faster or slower.

But in addition, the ability of the body to withstand and repair damages either from within or without would also play an appreciable role. This is of clinical relevance to gerontology because it is foreseeable that we should be able to further influence longevity by decreasing the effect of or exposure to damaging substances. We may also be able to influence the ability of the body to repair itself. The longevity of our current population represents the impact of such approach. Sanitation, improved diet, chemotherapy of infectious disease and treatment of heart disease may be looked upon as factors that have decreased background noise and allow our genetic tapes to play a little longer. Whether or not we will be able to influence the genetic message directly is highly speculative; however, the future for research on the cellular aspects of aging is exciting.

What Are Some of the Perplexing Questions Remaining?

It is not known why variations in aging exist from species to species. It has been proposed that metabolic rate may account for such differences.[24]

Furthermore, as mentioned, it is known that normal cells in tissue culture have a finite life span of approximately 50 doublings. After this point cellular growth slows and eventually stops. Where the "biological clock" resides is unknown. One cell line escapes this phenomenon and appears to have an infinite life span. This is the malignantly transformed tumor cell. Thus, understanding why normal cells are finite should lead to understanding of why some cells become malignant. Another cellular event of great interest and importance is the progressive loss of immunological function which occurs with age.[25] With aging there occurs an inability of T lymphocytes to maximally proliferate. In addition there occurs an increase in T lymphocytes with the ability to suppress other immunological cells. Finally, the number of normal T lymphocytes decreases with age. This may not only explain the predisposition to infection that occurs with age, but it may also suggest that decreased immunological surveillance leads to the development of malignant clones of cells within the body. In fact, the progressive weakening of the thymus-dependent immune system has led to the suggestion that the thymus itself serves as an "organ clock" to determine longevity.[26]

Other questions relative to the determination of aging include the following. What are the specific genes that control aging? What are the mechanisms by which mutagenesis of cells occurs? What controls the rates and mechanisms of synthesis of nucleic acids, cellular enzymes, structural proteins and cell membranes? What are the mechanisms by which cells are damaged and how does repair take place? What role do slow or latent viruses play in biological aging?

How Will We Explore the Cellular Basis of Aging?

Aging is an extremely active area of investigation and many approaches are currently being used. Animal colonies allow us to study the process of aging in a telescoped time frame within an environment protected from external insult. These colonies offer a means by which perplexing and fascinating observations of aging may be studied. For instance, it has been found that experimental animals fed a calorically restricted diet live appreciably longer than animals allowed free access to food.[27] Why this occurs is unknown.

Tissue culture is a technique by which the basic cellular function itself may be investigated. Changes in metabolism, alterations of cell morphology and the effect of potentially damaging agents both within and external to the cell may be studied. With techniques of recombinant DNA the genetic information of the cell itself may be probed and its regulation investigated. For instance, it has been found that the introduction of the sarcoma virus gene into normal cells endows them with immortality.[28] The exact functional method by which this occurs remains to be elucidated.

Finally, certain "model diseases" are being utilized as methods to understand many phenomena including aging. Syndromes of premature aging include Hutchinson-Gilford progeria, Werner's syndrome and Hallerman-Streiff syndrome. Furthermore, one of the most facinating aspects of Down's syndrome is its association with premature aging.[29] It has been noted that persons with Down's syndrome who survive into the later decades of life tend to die younger than other persons with mental handicaps. In addition, in such adults with Down's syndrome a progressive dementia develops superimposed upon their amentia. Clinically and pathologically this closely resembles the finding in Alzheimer's disease.[30] This association between Down's syndrome and senility is made even more intriguing by the epidemiological demonstration of the familial clustering of Alzheimer's disease, malignancy and birth of children with Down's syndrome.[31]

It is possible that the relationship between aging and Down's syndrome may also extend to changes in immunological function. Disorders of immune function occur in both conditions. An imbalance of resting levels of cyclic nucleotides cyclic adenosine 3′,5′-monophosphate (CAMP) and cyclic guanosine 3′,5′-monophasphate (CGMP) and their generating enzymes has been found in T cells of both normal aged patients and those with Down's syndrome.[32] It is speculated that this finding may help to explain immune dysfunction that occurs with aging and the increased incidence of infection in patients with Down's syndrome.

Since this premature senility and changes in immunological function in Down's syndrome appear to be entirely due to the excess of a particular portion of chromosome 21 (the distal q22 band),[33] it is reasonable to conclude that if one could understand the nature of this genetic information then one would have insight into why premature aging occurs in patients with Down's syndrome. This information would have relevance to our understanding of aging in general.

Thus, while the cellular basis of aging still remains highly speculative, excellent theories exist from which rational experiments are currently being conducted. The techniques of modern day biology are allowing such investigations to be carried out at a rate faster than any other time in history. These studies will allow better strategies for caring for the elderly and perhaps increasing human longevity. Whether or not biogerontology will allow us to "tamper with our biological clocks" is at best uncertain.[34] It can be envisioned that decrease in damage to the cell would allow us to live a full life expectancy and then die suddenly in the ninth decade when our genetic time "runs out." Perhaps we will be able to even reset the clock. But this would certainly lead to further problems. Should the clock be allowed to run longer? Should the clock be reset at a particular development stage? If so, where? The period of maximal production and enjoyment can occur throughout human life.[35] Because of the potential of scientific inquiry to lead to understanding of biological phenomena, the day may come when such questions have more than just potential relevance.

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